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L2: Entry 1 of 5 File: DWPI Sep 18, 2002

DERWENT-ACC-NO: 1999-155200
DERWENT-WEEK: 200317

TITLE: New CCR-3 antagonist piperazine derivatives and analogues - used for treating eosinophilic granulocyte-mediated inflammatory or allergic diseases, especially asthma

INVENTOR: GONG, L; KERTESZ, D J ; SMITH, D B ; TALAMAS, F X ; WILHELM, R S ; KERTESZ, J ; KONG, R Y

PATENT-ASSIGNEE: HOFFMANN LA ROCHE & CO AG F (HOFF), HOFFMANN LA ROCHE F (HOFF), SYNTEX USA LLC (SYNT)

PRIORITY-DATA: 1997US-056001P (August 18, 1997), 1998US-0134013 (August 14, 1998), 1998US-0197282 (November 20, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
KR 339460 B	September 18, 2002		000	C07D295/04
DE 19837386 A1	February 25, 1999		059	C07D295/13
EP 903349 A2	March 24, 1999	E	000	C07D295/12
FR 2767826 A1	March 5, 1999		000	C07D295/13
CZ 9802566 A3	March 17, 1999		000	C07D207/06
NO 9803749 A	February 19, 1999		000	C07D295/14
GB 2330580 A	April 28, 1999		000	C07D211/18
AU 9880800 A	February 25, 1999		000	C07D295/13
ZA 9807448 A	April 28, 1999		113	C07D000/00
CA 2245043 A	February 18, 1999		000	C07D295/15
CN 1211572 A	March 24, 1999		000	C07D295/12
HU 9801887 A2	June 28, 1999		000	C07D295/13
JP 11147872 A	June 2, 1999		054	C07D211/18
JP 3014367 B2	February 28, 2000		053	C07D211/18
SG 70110 A1	January 25, 2000		000	C07D211/18
NZ 331319 A	March 27, 2000		000	C07D211/26
KR 99023604 A	March 25, 1999		000	C07D295/04
BR 9803179 A	March 28, 2000		000	C07D295/027
MX 9806690 A1	July 1, 1999		000	C07D211/16
ES 2154167 A1	March 16, 2001		000	C07D211/18
ES 2154167 B1	November 1, 2001		000	C07D211/18
US 6323223 B1	November 27, 2001		000	A61K031/449
US 6339087 B1	January 15, 2002		000	A61K031/495
IT 1304150 B	March 8, 2001		000	C07D000/00
AU 744059 B	February 14, 2002		000	C07D295/13

DESIGNATED-STATES: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
KR 339460B	August 14, 1998	1998KR-0033037	
KR 339460B		KR 99023604	Previous Publ.
DE 19837386A1	August 18, 1998	1998DE-1037386	
EP 903349A2	August 10, 1998	1998EP-0114971	
FR 2767826A1	August 18, 1998	1998FR-0010504	
CZ 9802566A3	August 13, 1998	1998CZ-0002566	
NO 9803749A	August 17, 1998	1998NO-0003749	
GB 2330580A	August 17, 1998	1998GB-0017910	
AU 9880800A	August 18, 1998	1998AU-0080800	
ZA 9807448A	August 18, 1998	1998ZA-0007448	
CA 2245043A	August 14, 1998	1998CA-2245043	
CN 1211572A	August 18, 1998	1998CN-0117990	
HU 9801887A2	August 17, 1998	1998HU-0001887	
JP 11147872A	August 18, 1998	1998JP-0231918	
JP 3014367B2	August 18, 1998	1998JP-0231918	
JP 3014367B2		JP 11147872	Previous Publ.
SG 70110A1	August 18, 1998	1998SG-0003133	
NZ 331319A	August 11, 1998	1998NZ-0331319	
KR 99023604A	August 14, 1998	1998KR-0033037	
BR 9803179A	August 18, 1998	1998BR-0003179	
MX 9806690A1	August 18, 1998	1998MX-0006690	
ES 2154167A1	August 14, 1998	1998ES-0001760	
ES 2154167B1	August 14, 1998	1998ES-0001760	
US 6323223B1	August 18, 1997	1997US-056001P	Provisional
US 6323223B1	August 14, 1998	1998US-0134013	
US 6339087B1	August 18, 1997	1997US-056001P	Provisional
US 6339087B1	August 14, 1998	1998US-0134013	CIP of
US 6339087B1	November 20, 1998	1998US-0197282	
IT 1304150B	August 18, 1998	1998IT-MI01902	
AU 744059B	August 18, 1998	1998AU-0080800	
AU 744059B		AU 9880800	Previous Publ.

99023604 A INT-CL (IPC): A61 K 31/34; A61 K 31/36; A61 K 31/40; A61 K 31/435; A61 K 31/44; A61 K 31/445; A61 K 31/449; A61 K 31/47 ; A61 K 31/495; A61 K 31/496; A61 K 31/55; A61 P 1/00; A61 P 11/00; A61 P 17/00; A61 P 29/00; A61 P 37/08 ; A61 P 43/00; C07 D 0/00; C07 D 207/06; C07 D 207/09; C07 D 207/20; C07 D 207/325; C07 D 209/08; C07 D 209/10; C07 D 209/14; C07 D 209/20; C07 D 209/26; C07 D 209/42; C07 D 211/06; C07 D 211/10; C07 D 211/16; C07 D 211/18; C07 D 211/26; C07 D 211/30; C07 D 211/32; C07 D 213/36; C07 D 213/81; C07 D 213/82; C07 D 215/12; C07 D 215/48; C07 D 215/54; C07 D 223/04; C07 D 241/04; C07 D 243/08; C07 D 295/023; C07 D 295/027; C07 D 295/04; C07 D 295/10; C07 D 295/108; C07 D 295/12; C07 D 295/13; C07 D 295/135; C07 D 295/14; C07 D 295/15; C07 D 307/68; C07 D 307/71; C07 D 307/84; C07 D 307/85; C07 D 317/68; C07 D 333/00; C07 D 333/20; C07 D 333/24; C07 D 333/34; C07 D 333/38; C07 D 333/44; C07 D 333/58; C07 D 333/60; C07 D 333/68; C07 D 401/00; C07 D 401/02; C07 D 401/06; C07 D 401/12; C07 D 403/00; C07 D 405/00; C07 D 409/00; C07 D 409/12; C07 D 413/00; C07 D 417/00; C07 D 471/04; C07 D 473/00

ABSTRACTED-PUB-NO: DE 19837386A
BASIC-ABSTRACT:

NOVELTY - Di-(hetero)aryl-substituted pyrrolidine, piperidine, piperazine, perhydroazepine or perhydrodiazepine derivatives (I) are new.

AILED DESCRIPTION - Di-(hetero)aryl-substituted N-heterocyclic compounds of formula (I) and their precursors, vidual isomers, isomer mixtures and salts are new. T,U = N or CH, but not both CH; R1,R2 = H or alkyl; n = 0-2, provided T or U = CH if n = 0; m = 0-3; Ar1,Ar2 = aryl or heteroaryl; F' = alkylene, alkenylene or a bond, provided that if T = U = N d F' = alkylene, then R4 is not aryl; R = H or alkyl, or completes a carbocycle or heterocycle with R3 or R4; R3,R4 = H (but not both H), alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, heteroalkyl, CN or -alkylene-CO-Z; or CR3R4 = carbocycle or heterocycle; Z = alkyl, haloalkyl, alkoxy, haloalkoxy, OH, optionally mono- or disubstituted amino, aryl, aralkyl, aryloxy, aralkoxy, heteroaryl, heteroaryloxy or heteroaralkoxy; E = CONR5, SO2NR5, NR6CONR5, NR6SO2NR5, NR6CSNR5, NR6CO, NR6COO, OCONR6 or NR6SO2; R5 = H, alkyl, acyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heteroalkyl, heterocyclylalkyl, heterocycloalkylalkyl, heteroalkyl (sic) or -alkylene-CO-Z; or R5 completes heterocyclo-amino with R3 or R4; R6 = H, alkyl, acyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heteroalkyl or -alkylene-CO-Z; if T = N and E = CONR5, SO2NR5, NR6CONR5, NR6SO2NR5 or NR6CSNR5, then m is not 0; Q = -R7-W-R8-; R7 = 1-6C alkylene chain; R8 = bond or 1-4C alkylene chain; W = bond, CO, NR9, O, S, SO, SO2, CONR9, NR9CO, NR9SO2, SO2NR9, NR9CONR9, NR9SO2NR9 or NR9CSNR9; R9 = as R6; provided that if T = N and U = CH, then W is not CONR9.

INDEPENDENT CLAIMS are included for new intermediates of formula (IIg) and for the preparation of (I). X = NHR5, NHR6 or COOH.

USE - (I) have antiasthmatic, antiinflammatory, antiallergic and CCR-3 receptor antagonist activity.

(I) inhibit the recruitment of eosinophilic granulocytes by CCR-3 chemokines (e.g. RANTES, eotaxin, MCP-2, MCP-3 and MCP-4). They are useful for treating diseases mediated by eosinophilic granulocytes, such as inflammatory or allergic disease, including allergic respiratory tract diseases (e.g. asthma, allergic rhinitis, hypersensitive pulmonary disease or pneumonitis or eosinophilic pneumonia), inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), psoriasis and inflammatory dermatosis (e.g. dermatitis or eczema). (I) are especially used for treating asthma (claimed).

Daily dose is 0.05-20 (preferably 0.1-10) mg/kg, orally, parenterally or by inhalation.

N-(1(S)-(4-(3,4-Dichlorobenzyl)-piperazin-1-ylmethyl)-2-methylpropyl)-4-me- thylbenzamide dihydrochloride (Ia) had IC50 0.24 mu M for inhibition of 125I-eotaxin binding in CCR-3 transfixed L1.2 cells.

ADVANTAGE - (I) are free of the side-effects of prior art agents for treating eosinophilic granulocyte-mediated diseases (e.g. glucocorticoids).

ABSTRACTED-PUB-NO: US 6323223B
EQUIVALENT-ABSTRACTS:

NOVELTY - Di-(hetero)aryl-substituted pyrrolidine, piperidine, piperazine, perhydroazepine or perhydrodiazepine derivatives (I) are new.

DETAILED DESCRIPTION - Di-(hetero)aryl-substituted N-heterocyclic compounds of formula (I) and their precursors, individual isomers, isomer mixtures and salts are new. T,U = N or CH, but not both CH; R1,R2 = H or alkyl; n = 0-2, provided that T or U = CH if n = 0; m = 0-3; Ar1,Ar2 = aryl or heteroaryl; F' = alkylene, alkenylene or a bond, provided that if T = U = N and F' = alkylene, then R4 is not aryl; R = H or alkyl, or completes a carbocycle or heterocycle with R3 or R4; R3,R4 = H (but not both H), alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, heteroalkyl, CN or -alkylene-CO-Z; or CR3R4 = carbocycle or heterocycle; Z = alkyl, haloalkyl, alkoxy, haloalkoxy, OH, optionally mono- or disubstituted amino, aryl, aralkyl, aryloxy, aralkoxy, heteroaryl, heteroaryloxy or heteroaralkoxy; E = CONR5, SO2NR5, NR6CONR5, NR6SO2NR5, NR6CSNR5, NR6CO, NR6COO, OCONR6 or NR6SO2; R5 = H, alkyl, acyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heteroalkyl, heterocyclylalkyl, heterocycloalkylalkyl, heteroalkyl (sic) or -alkylene-CO-Z; or R5 completes heterocyclo-amino with R3 or R4; R6 = H, alkyl, acyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heteroalkyl or -alkylene-CO-Z; if T = N and E = CONR5, SO2NR5, NR6CONR5, NR6SO2NR5 or NR6CSNR5, then m is not 0; Q = -R7-W-R8-; R7 = 1-6C alkylene chain; R8 = bond or 1-4C alkylene chain; W = bond, CO, NR9, O, S, SO, SO2, CONR9, NR9CO, NR9SO2, SO2NR9, NR9CONR9, NR9SO2NR9 or NR9CSNR9; R9 = as R6; provided that if T = N and U = CH, then W is not CONR9.

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US 6339087B

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CHOSEN-DRAWING: Dwg.0/0

DERWENT-CLASS: B03
CPI-CODES: B07-H; B14-C03; B14-G02A; B14-K01A; B14-L06;